REMARKS

Interview

Applicants would like to thank Examiner Soroush and Supervisory Patent Examiner (SPE) Padmanabhan for the phone conference held with Applicants' representative on March 9, 2007. During the phone conference, the art rejections were discussed. Applicants' representative requested that the Examiners consider the discussion under MPEP 2131.03(II) regarding genus reference does not anticipates a later narrower species, if the reference does not disclose the species with sufficient specificity. SPE Padmanabhan agreed to consider MPEP 2131.03(II) with respect to the § 102 rejections when Applicants submit their response in writing.

Status of the Claims

Claims 33, 37-51, 53-57, 62, 64-66, 68, and 70-73, are withdrawn from consideration as being directed to a non-elected invention. Claims 58-61, 63, 67, 69, and 74 are currently under examination.

Double Patenting

Claims 58-61, 63, 67, 69, and 74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51-59 of copending application 10/519,193 and claims 1-15 of copending application 11/018,574.

Applicants respectfully point out that the claims of the present application requires associating an agent with a cationic component and optimizing the zeta potential of the composition comprising the agent and the cationic component, so that it is between about +30 mV to +60 mV. Applicants unexpectedly discovered that the optimal zeta potential for targeting a composition to an activated vascular site is +30 mV to +60 mV. The copending applications do not include the step of optimizing the zeta potential of the composition to between about +30 mV to +60 mV. The copending applications also do not disclose preparing the composition for targeting an activated vascular site. Thus, the claims in the present application and the copending applications are not obvious over each other.

Rejections Under 35 U.S.C. § 102(e)

Claims 58, 59, 61, 63, 67, 69, and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,770,222 ("Unger").

The claims of the present invention are directed to methods of modifying an agent to enhance its efficacy for targeting an activated vascular site comprising associating the agent with a cationic component and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, wherein the composition has a zeta potential in the range of about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5. The claims require that the size of the colloids in the composition to be between about 10 nm to about 400 nm. Moreover, Applicants unexpectedly discovered that +30 mV to about +65 mV is the optimal range of zeta potential for targeting an agent to an activated vascular site (figures 2 and 3). Thus, the claims of the present invention also require optimizing the zeta potential of the composition comprising the agent such that it is between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5.

The Office Action alleges that Unger anticipates the claimed invention because Unger discloses a method of preparing cationic liposomal compositions comprising a bioactive agent and having a particle size range between 30 nm to 5 μm and because the compositions of Unger inherently exhibits the same zeta potential. However, Unger only teaches methods of preparing cationic liposomal compositions having particles with a preferred mean diameter of between about 30 nm to about 5 μm. This range of mean diameter is much broader than what is claimed by the present invention and only overlaps with the range claimed by the present invention from 30 nm to 400 nm. Moreover, the overlap in the two ranges is less than 10% of the range disclosed by Unger.

Additionally, Unger does not teach methods of preparing compositions comprising zeta potential in the range of about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5, and Unger does not teach methods of preparing compositions for targeting activated vascular sites. Further, Unger does not include a step for obtaining a composition having an optimal zeta potential for targeting activated vascular sites. Since Unger is not directed to obtaining compositions for targeted delivery to activated vascular sites, Unger does not include the step of obtaining a composition having an optimal zeta potential of between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting activated vascular sites. Unger does not even disclose the zeta potential of the composition. Applicants respectfully point out when an agent is mixed with a cationic lipid to form a composition, the

composition can have various zeta potentials depending on the zeta potential of the agent and cationic lipid to begin with, the amount of each component in the composition, and the solution in which the components are formed. Accordingly, Unger does not include all the steps recited by the claimed method, and the compositions prepared by the method of Unger do not have the specific range of zeta potential recited in the claims.

MPEP 2131.03(II) states that in order to anticipate the claims, the reference must disclose the claimed subject matter with "sufficient specificity" and cites *Atofina v. Great Lakes Chemical Corp* for describing "sufficient specificity" as to constitute anticipation of the claims. In *Atofina*, the court concluded that an earlier genus reference does not anticipate a narrow species, if the prior art reference does not describe the narrower claimed range with sufficient specificity. *Atofina v. Great Lakes*, 78 USPQ2d 1417 (Fed. Cir. 2006). The court held that a prior art publication disclosing 100 °C to 500 °C for synthesizing difluoromethane does not anticipate a claimed method of synthesizing difluoromethane limited to the specific range of 330 °C to 450 °C, even though the prior art range is broader than and fully encompasses the claimed range. *Id.* at 1424. The court found that no reasonable fact finder could conclude that the prior art described the claimed range with sufficient specificity to anticipate the temperature range limitation recited in the claims. *Id.*

Similar to the fact situation in *Atofina*, Unger does not disclose a method of obtaining a liposomal composition having the recited particle size and zeta potential with sufficient specificity. Unger discloses obtaining a composition having particles with a diameter in the range of about 30 nm to 5 μm which is much broader than between 10 nm to 400 nm, the size of the particles recited in the claims. Also, Unger does not disclose optimizing the zeta potential of the liposomal composition to between +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5. Thus, Unger does not teach the range of the particle size or zeta potential recited in the claims with sufficient specificity to anticipate the claims. Accordingly, Unger does not teach or anticipate the claimed invention.

B. Claims 58, 59, 63, 67, 69 and 74 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,110,490 ("Thierry").

As discussed above, the claims are directed to modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM

KCl solution at about pH 7.5 for targeting an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm.

The Office Action alleges that Thierry anticipates the claimed invention because Thierry discloses methods of preparing drugs containing liposomes that are cationic. However, Thierry only teaches methods of preparing cationic liposomal compositions, wherein the diameter of the liposomes are between about 200 nm to about 3 μm. This range of diameter is much broader than what is claimed by the present invention and only overlaps with the range claimed by the present invention from 200 nm to 400 nm. Moreover, the overlap in the two ranges is less than 10% of the range disclosed by Thierry.

Additionally, Thierry does not teach methods of preparing compositions comprising zeta potential in the range of about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5, and Thierry does not teach methods of preparing compositions for targeting activated vascular sites. Thierry generally discusses delivery of the liposomal composition to various cells such as HeLa, NIH3T3, human embryonic kidney 293, and human vascular endothelial cells. However, Thierry does not include a step for obtaining a composition having an optimal zeta potential for targeting activated vascular sites. Thus, Thierry does not include the step of obtaining a composition having the optimal zeta potential of between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting activated vascular sites. Thierry does not even disclose the zeta potential of the composition. As discussed above, when an agent is mixed with a cationic lipid to form a composition, the composition can have various zeta potentials depending on the zeta potential of the agent and cationic lipid to begin with, the amount of each component in the composition, and the solution in which the components are formed. Accordingly, Thierry does not include all the steps recited by the claimed method, and the compositions prepared by the method of Thierry do not have the specific range of zeta potential recited in the claims.

Also, as discussed above, in *Atofina*, the court held that an earlier genus reference does not anticipate a narrow species, if the prior art reference does not describe the narrower claimed range with sufficient specificity. Like the fact situation in *Atofina*, Thierry does not disclose a method of obtaining liposomal compositions having the recited particle size and zeta potential with sufficient specificity. Thierry discloses obtaining a composition having particles with a diameter in the range of about 200 nm to 3 μm which is much broader than between 10 nm to 400 nm, the size of the particles recited in the claims. Also, Thierry does not disclose optimizing

the zeta potential of the liposomal composition to between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5. Thus, Thierry does not teach the range of the particle size or zeta potential recited in the claims with sufficient specificity to anticipate the claims. Accordingly, Thierry does not teach or anticipate the claimed invention.

Obviousness of the claims in view of Unger or Thierry

Applicants respectfully point out that neither Unger nor Thierry would render claims 58, 59, 61, 63, 67, 69, and 74 obvious because neither of these references discloses or suggests the recited size of the particles (10 nm to 400 nm) and the recited range of zeta potential (between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5). Moreover, the cited references do not provide motivation to modify the teachings of the references to include a step of obtaining a composition having the optimal range of zeta potential as recited by the claims for targeting an activated vascular site and for dispersing the composition in a medium to form colloidal particles having the size recited in the claims.

In general, the discovery of an optimum value in a known process is an obvious process. However, in *In re Antonie,* the court held that when the parameter optimized is not recognized to be a result-effective variable, optimization of that parameter is not an obvious step. *In re Antonie*, 195 USPQ 6 (CCPA 1977). Further, in *In re Soni*, the court held that Applicant's showing of substantial improved results for an invention and Applicant's statement that the results are unexpected are sufficient to establish unexpected results to overcome obviousness. *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). Prior to Applicants' discovery, it was not known that optimizing zeta potential would improve the efficacy of an agent in targeting an activated vascular site. Applicants unexpectedly discovered that the optimal range of zeta potential for targeting an activated vascular site is between about +30 mV to about +65 mV in about 0.05 mM KCl solution at about pH 7.5 (figures 2 and 3).

Accordingly, Unger and Thierry also do not render the claimed invention obvious.

Rejection Under 35 U.S.C. 103(a)

A. Claim 60 was rejected under 35 U.S.C. 103(a) as being unpatentable over Thierry or Unger.

Claim 60 is directed to a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a

composition having an optimal range of zeta potential and having an isoelectric point above 7.5 for targeting an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm. Applicants unexpectedly discovered that an isoelectric point above 7.5 improves targeting to activated vascular site.

Neither Thierry nor Unger discloses associating an agent with one or more cationic components to produce a composition having an optimal zeta potential for targeting an activated vascular site and having an isoelectric point above 7.5 and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm. Moreover, neither Unger or Thierry is directed to selectively targeting an activated vascular site and therefore neither references discloses a step for obtaining a composition having an optimal zeta potential for specific targeting to an activated vascular site and having an isoelectric point of about 7.5.

The Office Action appears to assume that Unger or Thierry inherently discloses the claimed zeta potential and isoelectric point of above 7.5 for targeting the composition to a vascular site (see the Office Action on page 7). However, Applicants respectfully point out that the claim is not directed to a product having a specific zeta potential and a specific isoelectric point. The claim is directed to a method of modifying an agent to enhance its efficacy to an activated vascular site comprising several steps. These references do not state or suggest obtaining a liposomal composition having an optimal zeta potential for targeting an activated vascular site and having an isoelectric point above 7.5. These references also do not state or suggest obtaining a liposomal composition comprising colloids having a size of about 10 nm to about 400 nm. Thus, there is no motivation to modify the method of Unger or Thierry to include the step of obtaining a liposomal composition having an isoelectric point above 7.5 and optimizing the zeta potential of the composition so that it is specific for targeting activated vascular site. Accordingly, neither Unger nor Thierry renders the claimed invention obvious.

The Office Action alleges that cationic lipids by definition must have an isoelectric point above 7, as defined in the specification at page 15, paragraph 57. However, when an agent is combined with a cationic component to form a composition, the composition does not necessarily have an isoelectric point above 7 because the agent may have a low isoelectric point to begin with. Nevertheless, the claim requires that the isoelectric point of the composition be above 7.5. Neither Unger nor Thierry suggests obtaining compositions having an isoelectric point above 7.5.

Accordingly, neither Unger nor Thierry renders the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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